Cognitive Enhancement

Pharmacologic, Environmental and Genetic Factors

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Academic Press is an imprint of Elsevier

Chapter 11

Cognitive Enhancement in Humans

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INTRODUCTION

Cognitive enhancement has become a trending topic in both academic and public debate. However, the discussants bring a very diverse background and motivation to this debate: The aim of many empirical researchers of cognitive enhancement is to understand the neurobiological and psychological mechanisms underlying cognitive capacities (McGaugh and Roozendaal, 2009), whereas theorists are rather more interested in their social and ethical implications (Savulescu and Bostrom, 2009). Whereas in basic research very specific mechanisms are studied (mostly in animal models), many theoretical discussions start from the counterfactual idea of a highly effective drug that makes its consumer super smart. In contrast to these thought experiments and to a plethora of data from animal studies, there is a surprising paucity of research that evaluates the effects of currently existing cognitive enhancers in healthy humans. A widely cited definition characterizes cognitive enhancement as interventions in humans that aim to improve mental functioning beyond what is necessary to sustain or restore good health (Juengst, 1998). While the current bioethical debate on cognitive enhancement shows a strong focus on pharmacological ways of enhancement, according to the given characterization, enhancement of mental capabilities also by nonpharmacological means has to be seen as proper for cognitive enhancement. In this chapter we aim to draw attention to several nonpharmacological cognitive enhancement strategies that have been largely neglected in the debate so far. We first summarize studies of the efficacy of psychopharmacological enhancers and then present data on the cognition-enhancing effects of a number of nonpharmacological methods. We start with broadly used interventions that are not commonly recognized as enhancement strategies, such as nutrition, physical exercise, and sleep, and then go over more specific methods such as meditation, mnemonic strategies, computer training,

Cognitive Enhancement. http://dx.doi.org/10.1016/B978-0-12-417042-1.00011-5

and brain stimulation technologies. We limit our review to methods that currently exist and do not speculate on future technologies.

PHARMACEUTICALS

Current debates on cognitive enhancement mainly concentrate on psychopharmaceuticals. In particular, psychostimulants are supposed to be widely used as cognitive enhancers (Talbot, 2009; Smith and Farah, 2011). Prescription stimulants such as amphetamines, modafinil, or methylphenidate (MPH) are thought to be the most frequently consumed "smart drugs," especially on college campuses, where, depending on the survey, 5–35% of healthy students report having consumed them for cognition enhancement purposes in the past year (for a meta-analysis see Wilens et al., 2008). In addition to use among students, MPH also is used in professions involving high cognitive performance and long periods of wakefulness, such as surgeons (Franke et al., 2013). While placebo-controlled trials support some of the claimed benefits for cognitive enhancers, it is worth noting that most of the claims have not been systematically tested. In addition to sparse evidence for efficacy, major concerns include adverse effects, toxicity, and the potential for addiction, especially because these drugs are often consumed without medical follow-up and in some cases over the long-term. Pharmacological cognitive enhancement has the potential to become a major public health concern. Recent publications on pharmacological cognitive enhancement focus mostly on the ethical debate rather than proof of effectiveness. On this background, some authors argue that research on efficacy and safety is or should be the rate-limiting step when considering the ethics of cognitive enhancement (Forlini et al., 2013). In the following, we briefly review data on the most common cognition enhancement drugs used in humans (see Table 11.1; for systematic reviews and meta-analyses see, e.g., Heishman et al., 2010; Repantis et al., 2010a,b).

Amphetamines. Amphetamines such Dexedrine® or Adderall® are sympathomimetic amines with central nervous system stimulant activity that have therapeutic properties and a long history of both medical and nonmedical use and abuse. The pharmacological effects of amphetamines have been attributed to their effects on central catecholamine neurotransmission, where they block reuptake from the synapse, inhibit the action of monoamine oxidase, and facilitate the release of dopamine and norepinephrine (Karoum et al., 1994; Wallace, 2012). Although it was thought that amphetamine use for nonmedical reasons was more widespread in the United States but less so in Europe (mainly because of the higher rates of prescriptions for attention deficit hyperactivity disorder treatment), a recent cross-sectional study suggested that in France amphetamines were used as frequently as MPH by medicine and pharmacology students for neuroenhancement purposes (Micoulaud-Franchi et al., 2014). The first review of the effects of amphetamines on the performance of healthy individuals was published in 1962 and concluded that 10 mg D-amphetamine

TABLE 11.1 Prescription Drugs Commonly Discussed as Cognitive Enhancers in Humans

	Indication/Off-label Use	Enhancement Efficacy	Common Side Effects	Addiction Potential
Amphetamines	Attention deficit hyperactivity disorder/narcolepsy, hypersomnolence, depression	Strong positive effects on verbal learning, delayed memory, vigilance and inhibitory control.	Dizziness, nervousness, headache, weight loss, hair loss, benign tachycardia, decreased libido; psychosis, severe cardiovascular adverse effects also possible	High
Methylphenidate	Attention deficit hyperactivity disorder/narcolepsy, hypersomnolence, depression	Evidence strongest for working memory; weaker for other memory domains and attention; some evidence for subjectively, but not objectively, measured vigilance.	Increased heart rate, headache, anxiety, nervousness, dizziness, drowsiness, insomnia; psychosis, severe cardiovascular adverse effects also possible	High
Modafinil	Narcolepy/ hypersomnolence, depression	Moderate positive effect on attention; no evidence for memory or mood; positive effects after moderate sleep deprivation; after prolonged sleep deprivation positive effects on wakefulness but not cognitive functions	Headache, dizziness, gastrointestinal complaints, increased diuresis, palpitations, nervousness, restlessness, and sleep disturbances such as insomnia; psychosis, severe cardiovascular adverse effects also possible	Unclear; most likely high
Acetylcholinesterase inhibitors	Mild to moderate dementia due to Alzheimer's disease	Sparse data and only on donepezil; controversial results, even (transient) negative effects found	Common first dose side effects: Bradycardia, nausea, diarrhea, decreased appetite, abdominal pain, vivid dreams, insomnia	Low
Memantine	Moderate to severe dementia due to Alzheimer's disease	No data from repeated dose trials available	Confusion, dizziness, drowsiness, headache, insomnia, agitation, and/ or hallucinations	Low

may hasten conditioning, increase the rate at which subjects may acquire proficiency in a motor skill, decrease discriminative reaction time (although more in fatigued subjects than in others), and improve coordination performances but do not improve intellectual performance in a more strict sense (Weiss and Laties, 1962). Since this work, several randomized controlled trials (RCTs) assessing cognitive performance of healthy adults after amphetamine administration have been conducted. Surprisingly, no meta-analysis of this data has been carried out to date. A large number of studies found a large positive effect of a D-amphetamine single-dose administration on verbal memory tasks, vigilance, learning, inhibitory control, and delayed memory rather than immediate/short-term memory. Conflicting results for the role of catecholamine-O-methyl-transferase polymorphism in amphetamine effects were found (Ilieva et al., 2013). However, studies with no effect can also be found, whereas a further concern should be the fact that in some of the studies with null findings the participants nevertheless believed their performance was better after taking an amphetamine than after taking a placebo, although the study was conducted in a double-blind manner (see, e.g., Ilieva et al., 2013). Common side effects of amphetamines include dizziness, nervousness, headache, weight loss, alopecia, benign tachycardia, and decreased libido. Psychosis can occur at therapeutic doses during chronic therapy as a treatment-emergent side effect (Berman et al., 2009). A US Food and Drug Administration warning on the packets of these drugs draws awareness to the risk of drug dependence, sudden death, and cardiovascular adverse effects (FDA, 2013). These serious potential side effects of these drugs make their use for enhancement purposes highly problematic.

Methylphenidate. MPH is a dopamine reuptake blocker that also enhances dopamine and norepinephrine release through pharmacologic mechanisms similar to those of amphetamines (Sulzer et al., 2005). A systematic review of the effects of these stimulants on healthy individuals showed that there is a lack of studies addressing this issue (Repantis et al., 2010b). The analysis of the few existing studies provided no consistent evidence for a general cognition-enhancing effect, though evidence for a positive effect on memory (mainly spatial working memory) was found. While such memory benefits seem to be in the large effect size range, the popular opinion that MPH enhances attention was not verified (Repantis et al., 2010b). Some studies even reported negative effects, such as a disruption of attentional control (Rogers et al., 1999). Further studies conducted after the publication of this systematic review provided some further positive results; however, it remains debatable whether these results are enough to support the far-fetched enthusiasm for MPH as cognitive-enhancing drug. Side effects in the majority of the trials of healthy individuals were rare and mostly benign, such as slightly increased heart rate, headache, anxiety, nervousness, dizziness, drowsiness, and insomnia. The long-term effects of MPH consumption on healthy adults, as well as on individuals previously treated for attention deficit hyperactivity disorder, are unknown, but no long-term neuronal toxicity has been described to date (Advokat, 2009).

Modafinil. The mechanisms of action of modafinil are not well understood but are believed to differ from those of MPH and amphetamines. Although there is mounting evidence that the drug's effects on dopamine and norepinephrine are primary, effects on γ-aminobutyric acid, glutamate, histamine, and orexin/hypocretin also are theorized (Volkow et al., 2009; Minzenberg and Carter, 2008; Ballon and Feifel, 2006). In a systematic review, modafinil was found to have mainly moderate enhancing effects, specifically on attention, among individuals who were not sleep deprived (Repantis et al., 2010b). No effect on memory, mood, or motivation was found in the few studies that examined these domains, but the results of the studies were not unequivocal. Newer studies seem to confirm these results. Moreover, there is evidence that the effect of modafinil depends to some extent on the individual's baseline performance (Randall et al., 2005). Adverse reactions to modafinil have been observed in very few cases in these trials of healthy individuals, primarily headache, dizziness, gastrointestinal complains (e.g., nausea, abdominal pain, dry mouth), increased diuresis, palpitations, nervousness, restlessness, and sleep disturbances and, especially in studies with non-sleep-deprived individuals, insomnia. Finally, because the majority of the studies that have been performed are short-term and single-dose studies, no conclusion on the reinforcing effects of, development of dependence on, and tolerance to modafinil in healthy individuals can be drawn.

Antidementia drugs. Prescription drugs currently available for the treatment of dementia provide a further possibility for cognitive enhancement in healthy individuals. Of interest are the drugs used for the treatment of dementia due to Alzheimer's disease, namely acetylcholinesterase inhibitors and memantine. The first category comprises three substances—donepezil, galantamine, and rivastigmine—that are recommended for clinical use for the treatment of patients with mild to moderate Alzheimer's disease (Racchi et al., 2004). Memantine is an *N*-methyl-D-aspartate receptor antagonist and is registered for the treatment of moderate to severe Alzheimer's disease (Sonkusare et al., 2005). Studies of antidementia drugs used for enhancement purposes in healthy individuals are sparse. In a systematic review (Repantis et al., 2010a), only 10 trials with donepezil, 1 with rivastigmine, and 7 with memantine have been reported. No RCTs examining the effects of galantamine in healthy individuals were found. Antidementia drugs show their effect in clinical populations after intake for several weeks; however, all the memantine and the one galantamine trial were single-dose trials. Repeated trials have been conducted only with donepezil. These were 6 small-scale trials lasting 14–42 days. Of these, only two had older persons as participants (Beglinger et al., 2005; Fitzgerald et al., 2008). The rest of the trials included young healthy participants. This factor complicates comparisons of the results and makes it difficult to generalize the results of the latter studies for the main population of interest, namely the growing elderly population. These few existing studies provide no consistent evidence for a cognitive enhancement effect. One study found that donepezil improved the retention of training on complex aviation tasks

(Yesavage et al., 2002). In another case, verbal memory for semantically processed words was improved (Fitzgerald et al., 2008). Donepezil might also improve episodic memory (Gron et al., 2005), but, interestingly, two studies reported transient negative effects on episodic memory (Beglinger et al., 2004, 2005). A newer study also found impaired working memory in older healthy participants taking donepezil for 6 weeks (Balsters et al., 2011). In a sleep deprivation study, donepezil had no effect when participants were well rested. Nevertheless, the memory and attention deficits resulting from 24 h of sleep deprivation were attenuated after donepezil intake. This effect, however, was seen only in individuals whose performance declined the most after sleep deprivation (Chuah and Chee, 2008; Chuah et al., 2009) and could not be confirmed in a recent study (Dodds et al., 2011). Of note, in most of the studies a large neuropsychological test battery was applied; however, an effect was shown using only one or few of the tests applied. This could speak either to a selective effect of donepezil or for small effects that in these relatively underpowered studies could be revealed in only one (maybe the most difficult) task. Another possible explanation could be that acetylcholinesterase inhibitors require pathologically diminished cholinergic transmission to show their effects; therefore, it is not possible to optimize performance in healthy individuals who already have an optimal concentration of acetylcholine. In conclusion, evidence for cognition-enhancing effects of currently available antidementia drugs in healthy subjects is sparse. In the majority of the trials, donepezil was well tolerated; however, some authors warn that sleep disturbances might become apparent in larger populations (Yesavage et al., 2002). Reported side effects were benign and led to dropouts only in a few cases. The adverse reactions were mainly gastrointestinal complaints (e.g., nausea) but also headache, dizziness, nightmares, and insomnia. For a comprehensive review of available treatment for Alzheimer's disease, please refer to Chapter 9 in this book.

NUTRITION

It has long been known that besides mere nourishment, some foods benefit our health more than others. In addition, in most cultures certain foods or dietary supplements are claimed to benefit cognitive capabilities. During recent years, an increasing number of studies have tested such claims for "functional foods" or isolated "nutraceuticals," and they indeed found cognition-enhancing effects of herbal products such as ginseng or bacopa (Neale et al., 2013), of ingredients such as omega-3 fatty acids (Luchtman and Song, 2013), or even of candies such as chocolate (Scholey and Owen, 2013) and chewing gum (although, in the latter, probably not because of its nutritional ingredients but because of the effects of chewing activity on enhancing alertness; see Scholey, 2004). The enhancing effects of two of the most common dietary constituents, namely caffeine and glucose, have been extensively studied and are briefly reviewed here.

Caffeine exerts its stimulating effects within less than an hour after administration. Caffeine is an adenosine receptor antagonist; it reduces inhibition of neural firing largely through increased turnover of noradrenaline in the brain (Smith et al., 2003; Ferre, 2008). Typical behavioral effects of caffeine include elevated mood, increased alertness, and increased sustained attention (Smith et al., 1991, 2005; Hewlett and Smith, 2007). It improves attention and reaction times (Warburton et al., 2001) and motor-skill performance on tasks that are impaired when arousal is low, for example, during driving simulations (Reyner and Horne, 1997). The effects of caffeine on more complex and cognitively demanding tasks are, however, controversial; both enhancing and impairing effects have been reported and probably depend on the dose administered (Kaplan et al., 1997; Rogers and Dernoncourt, 1998; Heatherley et al., 2005). The effects of caffeine on memory and learning are particularly disputed, and positive effects have been attributed to indirect effects from elevated arousal, mood, and concentration during encoding (Nehlig, 2010). However, it has recently been demonstrated that postencoding caffeine intake might also enhance certain aspects of memory (Borota et al., 2014).

It is debated whether and to what extent differences in prior caffeine consumption and their lack of experimental control contribute to the conflicting observations of cognition-enhancing effects of caffeine. Stronger enhancing effects of caffeine after short-term abstinence have been demonstrated during caffeine abstinence in some tasks for subjects with high versus low habitual caffeine intake (Smit and Rogers, 2000; Addicott and Laurienti, 2009). Caffeine tolerance has been demonstrated (Evans and Griffiths, 1992), and caffeine withdrawal in strong habitual consumers has been associated with headaches, increased subjectively perceived stress, feelings of fatigue, and reduced alertness (Ratcliff-Crain et al., 1989; Schuh and Griffiths, 1997; Dews et al., 2002; Juliano and Griffiths, 2004). Hence, positive effects of caffeine in studies with acutely abstinent habitual caffeine consumers might be explained, at least in part, through the reversal of withdrawal effects rather than the actual enhancement potential of caffeine. However, withdrawal effects also have been suggested to rely on psychological rather than pharmacological factors of reduced caffeine intake (Dews et al., 2002), and it has been shown that expectancy mimics effects of caffeine when consumers believe they consume a caffeinated beverage (Fillmore, 1994), thus further corroborating a psychological component of the caffeine effect following both consumption and withdrawal. In contrast, several studies demonstrate that caffeine yields similar effects when administered in a coffee, in a tea, or as a capsule, supporting a pharmacological rather than a psychological mechanism when participants' expectations are controlled for (Smith, 2002).

Glucose is the primary energy source for most organisms. Within minutes after glucose administration, a subjective increase in mental energy associated with higher glucose metabolism in the brain has been reported (Posner et al., 1988; Reivih and Alavi, 1983). Objective measures of cognitive performance demonstrate that glucose improves attention (Benton et al., 1994), reaction times (Owens and Benton, 1994), and working memory (Scholey et al., 2001), the latter occurring under conditions of high as well as under low glucose depletion (Owen et al., 2012; Jones et al., 2012). In contrast to caffeine, the most pronounced effects of glucose on cognition are found for declarative memory (Messier, 2004; Smith et al., 2011), where large effect sizes over a large range have been demonstrated, in particular for demanding tasks (e.g., Sünram-Lea et al., 2001, 2002a, 2002b; Meikle et al., 2004). High blood glucose concentrations are associated with improved memory function (Benton and Owens, 1993), and glucose administration before and after learning similarly improves memory performance, indicating that attentional or other non-memory-specific processes during encoding alone cannot be responsible for the memory-enhancing effects of glucose (Sünram-Lea et al., 2002a). Memory effects are more pronounced in elderly compared to young adults, and glucose tolerance was predictive for declarative memory performance (Manning et al., 1990; Meikle et al., 2004; Messier, 2004). On a neural level, the hippocampus has been proposed as the main brain region mediating the memory-enhancing effects of glucose; more specific mechanisms involve glucose effects on cerebral insulin, acetylcholine synthesis, potassium adenosine triphosphate channel function, and extracellular glucose availability in the brain (Smith et al., 2011).

In conclusion, there is evidence that caffeine and glucose enhance mood, subjectively perceived energy, vigilance, attention, and some aspects of memory and may even exert their effects in a synergistic fashion if administered together (Adan and Serra-Grabulosa, 2010). However, individual differences, for example, in glucose tolerance or nutritional habits such as caffeine consumption, influence the extent and direction of these effects.

PHYSICAL EXERCISE

It is common knowledge that regular physical activity is a highly beneficial factor for preventing cardiovascular diseases and staying healthy in general. In the first half of the twentieth century it was demonstrated that athletes outperform physically inactive individuals in cognitive functions as well (Burpee and Stroll, 1936), and an emerging body of evidence suggests that regular aerobic exercise indeed has beneficial effects on brain function and cognition (Hillman et al., 2008). Many studies of the effects of physical exercise on cognition focus on developmental issues, examining either children of different age groups or elderly adults. In school-age children, physical exercise was demonstrated to benefit, for example, academic achievement, intelligence, perceptual skills, and verbal and mathematical ability (Sibley and Etnier, 2002). In older adults with and without pathological cognitive decline, beneficial effects of various physical exercise programs on different aspects of cognition were observed (Richards et al., 2003; van Uffelen et al., 2008). A recent meta-analysis of RCTs demonstrated that aerobic exercise training improves attention, processing speed, executive function, and memory, whereas effects on working memory were less consistent (Smith et al., 2010). Even if methodological issues in measuring the effect of exercise on cognition, in particular for studies with elderly subject populations, remain (Miller et al., 2012; Hötting and Röder, 2013), the conclusion that physical activity helps to preserve mental abilities throughout aging seems to be warranted.

In contrast to research in children and older adults, there are fewer studies of the effects of physical exercise on the cognition of younger and middle-aged adults. Most data on these age groups can be found in studies of older adults, in which they were examined as control groups for comparison with the elderly. An exception to this pattern constitutes studies focusing not on the chronic effects of regular physical activity but on the acute effects of exercise. For example, brief bouts of physical exercise improved long-term memory in young adults (Coles and Tomporowski, 2008). Intense exercise in the form of high-impact anaerobic running was shown to strongly enhance learning speed in a vocabulary memorizing task (Winter et al., 2007). A recent meta-analysis demonstrated that mental speed in particular and memory processes are consistently enhanced after acute exercise, whereas the effects during acute exercise seem to depend on the specific exercise mode and cognitive domain; attention and certain memory and executive function tasks show the strongest effects (Chang et al., 2012). In general, however, cognition-enhancing effects of acute exercise seem to be in the small to medium range (Lambourne and Tomporowski, 2010; Chang et al., 2012). In addition to motivational factors, an increase in general arousal level related to physical exertion has been hypothesized as a potential mechanism (Brisswalter et al., 2002); however, increased oxygenation of the frontal cortex also has been discussed as a mechanism underlying the cognition-enhancing effects of acute exercise (Yanagisawa et al., 2010; Ando et al., 2011; Endo et al., 2013).

Data on specific neural mechanisms underlying the effects of physical exercise on human cognition are rather sparse. Regular physical exercise training improved resting functional efficiency in higher-level cognitive networks including the frontal, posterior, and temporal cortices of older training participants compared a control group (Voss et al., 2010). In particular, greater task-related activity in frontoparietal networks is associated with effects of both general cardiovascular fitness and exercise training on cognition (Colcombe et al., 2004). In addition, hippocampal cerebral blood flow and hippocampal connectivity exhibited significant increases through physical exercise (Burdette et al., 2010). Structurally, cardiovascular fitness within the healthy elderly correlates with areas of preserved gray matter that typically show age-related decline (Gordon et al., 2008); in particular, hippocampal volume was found to be positively correlated with physical fitness in older adults (Erickson et al., 2009) as well as in children (Chaddock et al., 2010). Significant brain volume increases in both gray and white matter regions also were demonstrated to be associated with aerobic exercise training (Colcombe et al., 2006). In particular, the size of the anterior hippocampus was shown to increase through physical exercise; this increase was related to enhanced spatial memory and increased serum concentrations of brain-derived neurotrophic factor (BDNF), a mediator of hippocampal neurogenesis in the dentate gyrus (Ericksson et al., 2011). This is in line with data derived from animal models, showing that physical exercise increases BDNF gene expression in the hippocampus (Neeper et al., 1995) and that hippocampal BDNF indeed mediates the effects of physical exercise on cognition (Vaynman et al., 2004; Gomez-Pinilla et al., 2008). Also, the enhancing effects of intense acute exercise seem to be mediated by BDNF increases (Winter et al., 2007). Finally, parallel studies of mice and humans demonstrated that cerebral blood volume measurements provide an imaging correlate to neurogenesis in the dentate gyrus and that physical exercise had a primary effect on cerebral blood volume in the dentate gyrus that correlated with cognitive function (Pereira et al., 2007). In conclusion, there is converging evidence at several levels of observation that physical exercise enhances cognitive function throughout the lifespan; however, acute and long-term physical exercise might exert differential effects on different cognitive functions (Roig et al., 2013).

SLEEP

Humans spend a third of their lifetime asleep. From an evolutionary standpoint, this phenomenon helps to save energy—but it also leaves the sleeper in a potentially dangerous state of inattention. Sleep, therefore, has to provide the organism with important advantages to compensate for this disadvantage. A rapidly growing body of literature suggests that an important function of sleep is to enhance cognitive capacities, in particular memory (Diekelmann and Born, 2010) and creativity (Dresler, 2012).

The first empirical reports of the positive effects of postlearning sleep on memory consolidation were published almost a century ago: Jenkins and Dallenbach (1924) demonstrated that over retention periods including sleep, nonsense syllables are less prone to being forgotten compared to an equivalent period of wakefulness. Since then, hundreds of studies testing different memory systems have confirmed the positive effects of sleep on memory consolidation (Diekelmann and Born, 2010). It might be argued that regular sleep is just a general biological prerequisite to ensure cognitive functioning, and therefore sleep trivially favors memory consolidation compared to sleep deprivation. However, in experimental designs without sleep deprivation as a control condition, sleep positively affects memory consolidation compared to wakefulness, for example, when retention intervals during the day are compared with nocturnal retention intervals of similar length (Fischer et al., 2002; Walker et al., 2002). Furthermore, a growing number of studies demonstrates that additional sleep in the form of daytime naps also benefits memory function in non-sleep-deprived subjects (e.g., Mednick et al., 2003; Korman et al., 2007). Of note, even a nap as short as 6 min has been shown to be sufficient to promote memory performance

(Lahl et al., 2008), and for some memory systems the benefit of a daytime nap is comparable to a whole night of sleep (Mednick et al., 2003). In general, the size of the sleep effect on memory consolidation seems to depend on the involved memory system: whereas for declarative learning, effect sizes of sleep are in the medium range (e.g., Gais et al., 2006), sleep effects on procedural or perceptual learning are large (Fischer et al., 2002) or very large (Karni et al., 1994). In addition to its stabilizing function, sleep boosts certain kinds of memories even above the level of initial acquisition; procedural memories such as motor skills typically reach a plateau after some time of training, but after a night of sleep motor performance starts from a higher level despite the absence of further training (Walker et al., 2002). Interestingly, the sleep–memory relationship is specifically influenced by personal factors such as gender, hormonal status, or mental health (Dresler et al., 2010; Genzel et al., 2012).

The neural mechanisms underlying the effects of sleep on memory consolidation are still poorly understood. A major point of discussion is the question of whether newly formed memories profit from rather passive homeostatic processes (Tononi and Cirelli, 2003) or are actively consolidated during sleep. While several animal studies demonstrated a neuronal replay of activation patterns during sleep that were associated with recent memories (Wilson and McNaughton, 1994; Ji and Wilson, 2007), a study of humans using memory-related odor cues during sleep could demonstrate a causal role of sleep for memory consolidation (Rasch et al., 2007). For several years it was thought that rapid eye movement (REM) sleep supports the consolidation of procedural memories, whereas non-REM sleep supports declarative memories such as verbal information; however, recent studies suggest that this model was too simplistic (Genzel et al., 2009; Rasch et al., 2009; Dresler et al., 2011). Instead of global sleep stages, the role of physiological microprocesses during sleep gained attention. In particular, the interaction of hippocampal sharp wave ripples, thalamocortical sleep spindles, and cortical slow oscillations is thought to play a key physiological role in the consolidation of memories (Genzel et al., 2014).

Anecdotal reports of scientific discovery, inventive originality, and artistic productivity suggest that creativity can also be triggered or enhanced by sleep. Several studies confirm these anecdotes, showing that sleep promotes creative problem solving compared with wakefulness. For example, when subjects performed a cognitive task that could be solved much faster by applying a hidden rule, after a night of sleep more than twice as many subjects gained insight into the hidden rule when compared with a control group that stayed awake (Wagner et al., 2004). Like sleep-related memory enhancement, active processes during sleep seem to promote creativity. If applied during sleep, olfactory stimuli that were associated with creativity tasks before sleep trigger insights overnight (Ritter et al., 2012). In particular, REM sleep, the sleep stage most strongly associated with intense dreaming, enhances the formation of associative networks in creative problem solving (Cai et al., 2009). Selective deprivation of REM sleep but not of other sleep stages impairs postsleep performance on creativity tasks that are presented to the subjects before sleep (Cartwright and Ratzel, 1972; Glaubman et al., 1978). Subjects show greater cognitive flexibility in creativity tasks immediately after awakening from REM sleep compared with awakening from other sleep stages (Walker et al., 2002). However, slow-wave sleep also has recently been related to creative problem solving (Beijamini et al., 2014).

Both theoretical models and empirical research of creativity suggest that sleep is a highly effective creativity enhancer (Dresler, 2012). The historical standard model proposes a passive incubation phase as an essential step to creative insights (Helmholtz, 1896). Psychoanalytical models emphasize primary process thinking for creative cognitions that is explicitly conceptualized as dream-like (Kris, 1952). Cognitive models propose that flat association hierarchies and a state of defocused attention facilitate creativity (Mednick, 1962). Hyperassociativity and defocused attention are phenomenal features of most dreams and physiologically are probably caused by deactivation of the prefrontal cortex (Hobson and Pace-Schott, 2002). Physiological models suggest high variability in cortical arousal levels as beneficial for creativity (Martindale, 1999), and the sleep cycle can be considered a prime example of such arousal variability. The chaotic activation of the cortex during REM sleep through brain stem regions in the absence of external sense data leads to a much more radical renunciation from unsuccessful problem-solving attempts, leading to coactivation of cognitive data that are highly remote during waking life. These coactivations, woven into a dream narrative in a self-organizing manner, repeatedly receive further innervations by the brain stem, leading to bizarre sequences of loosely associated dream topics that might eventually activate particular problem-relevant cognitions or creative cognitions in general (Hobson and Wohl, 2005). In conclusion, the phenomenological and neural correlates of sleep provide ideal incubation conditions for the genesis of creative ideas and insights.

MEDITATION

Meditation has been conceptualized as a family of complex emotional and attentional regulatory training regimes (Lutz et al., 2008). Such approaches include ancient Buddhist mindfulness meditations such as Vipassana and Zen meditations, as well as several modern group-based standardized meditations (Chiesa and Malinowski, 2011). Two rather traditional approaches are the focus of current research: focused attention meditation and open monitoring meditation, which involve voluntary focusing of attention on a chosen object or nonreactive monitoring of the content of experience from moment to moment (Lutz et al., 2008). During recent years, the effects of meditation practice also were systematically studied in western laboratories, and a rapidly growing body of evidence demonstrates that meditation training enhances attention and other cognitive capacities. For example, in comparisons of experienced meditators with meditation-naive control subjects, meditation practice has been associated with increased attentional performance and cognitive flexibility (Moore and Malinowski, 2009; Hodgins and Adair, 2010). In longitudinal studies, 3 months of meditation training could be shown to enhance attentional capacity (Lutz et al., 2009), perception, and vigilance (MacLean et al., 2010). Even a brief training of just four meditation sessions was sufficient to significantly improve visuospatial processing, working memory, and executive functioning (Zeidan et al., 2010). A recent systematic review associated early phases mindfulness meditation training with significant improvements in selective and executive attention, whereas later phases were associated with improved sustained attention abilities. In addition, meditation training was proposed to enhance working memory capacity and some executive functions (Chiesa et al., 2011). A recent meta-analysis of the effects of meditation training reported medium to large effect sizes for changes in emotionality and relationship issues, medium effect sizes for measures of attention, and smaller effects on memory and several other cognitive capacities (Sedlmeier et al., 2012).

The neurophysiological mechanisms underlying meditation practice and its relation to cognition also have been addressed. Electroencephalographic (EEG) studies revealed a significant increase in alpha and theta activity of subjects who underwent a meditation session (Kasamatsu and Hirai, 1966; Murata et al., 1994). Neuroimaging studies showed that meditation practice activates or deactivates brain areas comprising the prefrontal cortex and the anterior cingulate cortex (Hölzel et al., 2007), the basal ganglia (Ritskes et al., 2003), the hippocampus, the pre- and postcentral gyri, as well as the dorsolateral prefrontal and parietal cortices (Lazar et al., 2000). Focusing on attention studies, it has been demonstrated that long-term meditation supports enhanced activation of specific brain areas while also promoting attention sustainability (Davidson et al., 2003). Different studies also emphasized the role of meditation as a mental process that modulates plasticity in neural circuits commonly associated with attention (Davidson and Lutz, 2008). Functional magnetic resonance imaging studies also demonstrated a reduction of neural responses in widespread brain regions that are linked to conceptual processing, which suggests enhanced neural efficiency, probably via improved sustained attention and impulse control (Pagnoni et al., 2008; Kozasa et al., 2012). Moreover, positron emission tomography studies demonstrated increased dopamine release in the ventral striatum as a result of yoga meditation, which in turn suggests regulation of conscious states at the synaptic level (Kjaer et al., 2002). In addition, some studies have suggested that meditation practice is associated with structural brain changes. Compared with meditation-naive control subjects, long-term meditators showed significantly larger volumes of the right hippocampus and orbitofrontal cortex (Luders et al., 2009) and significantly greater cortical thickness in brain regions associated with attention, interoception, and sensory processing, including the prefrontal cortex and right anterior insula (Lazar et al., 2005). In a longitudinal study with meditation-naive subjects undergoing an 8-week meditation program, gray matter increases in the hippocampus and other brains regions could be observed (Hölzel et al., 2011).

MNEMONIC STRATEGIES

In modern society, the ability to cope with verbal or numerical information becomes increasingly important. However, our learning skills evolved to handle concrete visuospatial rather than abstract information. While we can easily remember our last birthday party in great detail and typically do not have any problems recalling a once-walked route including dozens or even hundreds of single sights and branches, most of us have a very hard time memorizing telephone numbers, foreign vocabularies, or shopping lists. The most common way to memorize such information is rote learning: We take up the information to be remembered into our short-term memory and repeat it over and over again. However, such a procedure is slow and inefficient, in particular because of a severe limitation of short-term memory capacity. As Miller (1956) observed more than half a century ago, an average human can hold seven (plus or minus two) chunks of arbitrary information in short-term memory. In contrast, a few individuals show memory skills far beyond this normal range. A century ago some case reports mention exceptional memorizers with memory spans of several dozen digits (Brown and Deffenbacher, 1975). In a seminal case study, a normal college student was trained over the course of 2 years, eventually reaching a memory span of 82 digits read at the pace of one digit per second (Ericsson et al., 1980). Since the early 1990s, the top participants of the annual World Memory Championships regularly prove memory spans of hundreds of digits (Konrad and Dresler, 2010). However, such superior memorizers do not seem to exhibit structural brain changes or superior cognitive abilities in general; they acquired their skills by deliberate training in the use of mnemonic techniques (Brown and Deffenbacher, 1988; Maguire et al., 2003; Ericsson, 2009; Dresler and Konrad, 2013).

To cope with the limitations of natural memory, humans have always used external remembering cues (D'Errico, 2001). The term *mnemonics* is typically used to denote internal cognitive strategies aimed at enhancing memory. Parallel to their success in memory artistry and memory sports, several mnemonics have been shown to strongly enhance memory capacity in scientific studies (Bellezza, 1981; Worthen and Hunt, 2011a,b). The most prominent is probably the so-called method of loci, an ancient technique used extensively by Greek and Roman orators (Yates, 1966). It uses well-established memories of spatial routes: during encoding, to-be-remembered information items are visualized at salient points along such a route, which in turn is mentally retraced during retrieval. A second powerful mnemonic is the phonetic system, which is designed to aid the memorization of numbers: single digits are converted to letters, which are then combined to form words. Both the method of loci and the phonetic system have been shown to be very effective and even increase their efficacy over time, that is, at delayed recall after several days compared to immediate recall (Bower, 1970; Roediger, 1980; Bellezza et al., 1992; Hill et al., 1997; Higbee, 1997; Wang and Thomas, 2000). A third mnemonic that has been shown to be effective is the keyword method, designed specifically to enhance the acquisition of foreign vocabulary (Raugh and Atkinson, 1975) but also helps with learning scientific terminology (Rosenheck et al., 1989; Brigham and Brigham, 1998; Balch, 2005; Carney and Levin, 1998). It associates the meaning of a to-be-remembered term with what the term sounds like in the first language of the learner.

A recently published broad overview of mnemonics demonstrates that research into these techniques has lost attention since 1980 (Worthen and Hunt, 2011b). In particular, neurophysiological data on mnemonics is sparse. A seminal study of expert mnemonics users found that during mnemonic encoding brain regions that are critical for spatial memory—in particular parietal, retrosplenial, and right posterior hippocampal areas—are engaged (Maguire et al., 2003). Likewise, the superior digit memory of abacus experts was associated specifically with brain regions that process visuospatial information(Tanaka et al., 2002). Here, abacus skill can be interpreted as a mnemonic for memorizing digits. In two studies with novices taught in the method of loci, mnemonic encoding led to increases in the activation of prefrontal and occipitoparietal areas in particular, whereas mnemonic-guided recall led to increases in the activation of left-sided areas in particular, including the parahippocampal gyrus, retrosplenial cortex, and precuneus (Nyberg et al., 2003; Kondo et al., 2005).

Another strategic method to enhance memory retention that has gained attention in recent years is retrieval practice. While retrieval of learned information in testing situations is traditionally thought to simply assess learning success, repeated retrieval itself has been shown to be a powerful mnemonic enhancer, producing large gains in long-term retention compared with repeated studying (Roediger and Butler, 2011). For example, when students have to learn foreign vocabulary words, repeated studying after the first learning trial had no effect on delayed recall after 1 week, whereas repeated testing produced a surprisingly large effect on long-term retention (Karpicke and Roediger, 2008). In addition to learning vocabulary, text materials also profit from repeated retrieval (Roediger and Karpicke, 2006; Karpicke and Roediger, 2010). Interestingly, study participants seem to be unaware of this effect, overestimating the value of repeated study and underestimating that of repeated retrieval (Roediger and Karpicke, 2006; Karpicke and Roediger, 2008). Effects of retrieval practice were even shown to produce greater success in meaningful learning than elaborative studying strategies, which are designed to lead to deeper learning and therefore hold a central place in contemporary education (Karpicke and Blunt, 2011). On the neural level, repeated retrieval leads to higher brain activity in the anterior cingulate cortex during retest, which was interpreted as an enhanced consolidation of memory representations at the systems level (Eriksson et al., 2011).

In conclusion, mnemonics strategies can be seen as strong and reliable enhancers of learning and memory capacity. While their immediate benefits for easy-to-learn material seem to be have a small to medium effect size, the effectiveness of mnemonics strikingly grows with task difficulty or retention time and can reach effect sizes in terms of Cohen's d of larger than 3 or 4 (e.g., Higbee, 1997; Karpicke and Roediger, 2008). Of note, the benefits of mnemonics in population groups with particular cognitive training needs, as, for example, in age-related cognitive decline, seem to be less pronounced (Verhaeghen et al., 1992), but they still can reach large effect sizes if memory is assessed after prolonged retention time (Hill et al., 1997).

COMPUTER TRAINING

In addition to the acquisition of mnemonic strategies, the ubiquitous availability of modern computer technology has prompted more straightforward training of cognitive capabilities: cognition-enhancing effects of both recreational and experimental use of computer games and brain training programs have gained increasing attention in recent years. Computer programs allow repeated and highly controlled training of various cognitive capabilities; their game-like nature often is experienced as intrinsically rewarding by the participants. Because enhanced performance on the specific computer program is rather unsurprising, the main goal of many scientific studies of computerized cognitive training is to investigate a potential transfer of effects to other tasks and cognitive domains.

Whereas potential societal effects of the popularity of video games have generated concern among parents, practitioners, and politicians (Anderson et al., 2010), their potential to train perceptual skills also has been emphasized (Achtman et al., 2008; Hubert-Wallander et al., 2011). Compared to nongamers, regular video gamers show improvements in cognitive flexibility (Colzato et al., 2010), enumeration ability (Green and Bavelier, 2006), visual search (Castel et al., 2005), visual attention (Green and Bavelier, 2003), and psychomotor skills (Kennedy et al., 2011). While several video games have been found to improve mental rotation (Okagaki and Frensch, 1994), contrast sensitivity (Li et al., 2009), spatial visual resolution (Green and Bavelier, 2007), and task-switching abilities (Strobach et al., 2012) among nongamers, other studies with naive subjects found no training improvement of cognitive capabilities in which video gamers excelled (Boot et al., 2008).

In addition to recreational video games, a rapidly increasing number of studies tests computerized training programs specifically targeting certain cognitive domains such as memory (Mahncke et al., 2006; Schmiedek et al., 2010; Zelinski et al., 2011), attention (Smith et al., 2009), executive function, and processing speed (Nouchi et al., 2012) in different age groups. Working memory is a cognitive domain that has garnered particular attention in recent years. Measures of working memory correlate strongly with intelligence, and both capabilities have been considered very stable. In recent years, however, several studies of children (Thorell et al., 2009; Nutley et al., 2011) and adults (Jaeggi et al., 2008, 2010) found that training with adaptive versions of working memory tasks such as the n-back task not only improves working memory but also shows transfer to fluid intelligence measures. However, replication of such transfer effects has proved difficult (Dahlin et al., 2008; Holmes et al., 2010; Redick et al., 2013) and hence has been questioned by some authors (Shipstead et al., 2010). Explanations for these inconsistent findings include individual differences in training performance (Jaeggi et al., 2011) and different types of training (strategy versus "core" working memory training) potentially having different transfer effects (Morrison and Chein, 2011). In general, the problem of transfer to tasks and cognitive domains not directly trained is a major issue in cognitive training programs (Fuyuno, 2007; Ackerman et al., 2010). For example, 6-week online study with a very large sample size did not find any evidence for transfer to nontrained tasks (Owen et al., 2010). A video game designed for the training of multitasking performance was recently demonstrated to have the potential to prompt transfer effects to untrained cognitive control abilities such as sustained attention and working memory (Anguera et al., 2013).

Even though commercial offers often overhype their efficacy, video games and computerized training programs are promising tools for cognitive enhancement because of their broad availability and self-motivating nature. Effect sizes of computerized training strongly depend on the cognitive domain trained and tested; processing speed and perceptual measures show medium to large effect sizes, whereas effects for different memory domains are only in the small or medium range (Mahncke et al., 2006; Smith et al., 2009; Schmiedek et al., 2010; Zelinski et al., 2011). Which forms of training produce reliable and strong transfer effects to relevant cognitive domains remains to be determined in future studies.

BRAIN STIMULATION

Since the introduction of electroconvulsive therapy for psychiatric disorders in the 1930s, several forms of invasive and noninvasive brain stimulation have been developed as a tool for enhancing brain function in health and disease (Hoy and Fitzgerald, 2010; McKinley et al., 2012; Guleyupoglu et al., 2013). Invasive methods for brain stimulation include deep-brain stimulation (DBS) and direct vagus nerve stimulation (dVNS). In DBS electrodes are implanted in deep-brain structures and used to modulate their activity through high-frequency stimulation. DBS of the hypothalamus (Hamani et al., 2008) and of the entorhinal area, but not of the hippocampus directly, have been demonstrated to enhance declarative learning (Suthana et al., 2012; Suthana and Fried, 2014). dVNS shows that stimulation of afferent vagal fibers seems to modulate the central nervous system, perhaps by stimulating brain stem structures (Krahl et al., 1998; Groves and Brown, 2005). dVNS has been shown to increase memory function (Clark et al., 1999), specifically memory consolidation (Ghacibeh et al., 2006). Devices for invasive brain stimulation require surgery (Kuhn et al., 2010; Ben-Menachem, 2001), and a significant number of patients with long-term DBS have hardware-related complications (Oh et al., 2002) in addition to complications from the initial surgery.

Since the 1990s, noninvasive brain stimulation techniques have become increasingly popular for the modulation and enhancement of cognitive capabilities in healthy subjects (Dayan et al., 2013). Transcranial magnetic stimulation (TMS) applies brief magnetic pulses through a coil to the scalp, thereby inducing electric currents in the brain. Different protocols including single-pulse, paired-pulse, and high- and low-frequency repetitive TMS have different cognitive effects, either interfering with or enhancing cognitive processes (Rossi and Rossini, 2004). TMS has been demonstrated to speed up encoding and retrieval by stimulating the left or right dorsolateral prefrontal cortex, respectively (Gagnon et al., 2010). TMS over the prefrontal cortex also sped up analogic reasoning but did not change the error rate (Boroojerdi et al., 2001). Furthermore, TMS delivered to the frontal or parietal lobe improved accuracy on the mental rotation task (Klimesch et al., 2003). Also, for procedural skills, an enhancement through TMS has been demonstrated, mainly by reducing intrahemispherical "rivalry" by inhibiting contralateral brain areas (Kobayashi et al., 2004; Bütefisch et al., 2004). Such disinhibition effects also have been used for phonological memory enhancement by reducing interference between similar-sounding words in phonological memory (Kirschen et al., 2006) and visuospatial attention enhancement on one side by impairing the other (Hilgetag et al., 2001; Thut et al., 2004). It has been suggested that TMS inhibition of frontotemporal regions induces savant-like abilities in drawing, mathematics, calendar calculating, number estimation, and proofreading (Young et al., 2004; Snyder et al., 2003, 2006).

In addition to TMS, several methods for transcranial electrical stimulation that change the voltage across neuronal membranes exist (for recent reviews see Paulus, 2011; Ruffini et al., 2013; Guleyupoglu et al., 2013). Transcranial direct current stimulation (tDCS) (for a comprehensive review see Chapter 12) sends a small electric current (typically 1–2 mA) between two electrodes placed on the scalp (Been et al., 2007). The technique seems to work by changing the likelihood of neural firing in superficial parts of the cortex; neurons under the anode neurons become depolarized and more excitable, while neurons under the cathode become hyperpolarized and less excitable. tDCS induces different effects depending on polarity and electrode placement, which can outlast the stimulation by more than an hour (Nitsche et al., 2005). tDCS has frequently been reported to enhance learning and memory (Chi et al., 2010; Clark et al., 2012; Javadi et al., 2011; Kincses et al., 2003; Reis et al., 2008). For example, tDCS of the left dorsolateral prefrontal cortex enhanced verbal learning (Javadi and Walsh, 2011; Javadi et al., 2011), whereas tDCS of the motor areas enhanced motor learning (Reis et al., 2009). tDCS during slow-wave sleep enhanced memory consolidation (Marshall et al., 2004), probably by boosting slow-wave oscillations (Marshall et al., 2006). Performance on working memory tasks also was found to be enhanced by tDCS (Fregni et al., 2005; Luber et al., 2007; Teo et al., 2011; Ohn et al., 2008). In addition to learning and memory, other cognitive capacities also were enhanced by tDCS, such as verbal fluency (Iyer et al., 2005), mathematical abilities (Cohen Kadosh et al., 2010; Iuculano and Cohen Kadosh, 2013), and reasoning in matchstick problems (Chi and Snyder, 2011). For a comprehensive review of tDCS please refer to Chapter 12 in this book.

In contrast to tDCS, transcranial alternating current stimulation (tACS) works with oscillating electrical currents. While sinusoidal stimulation is most common, other waveforms such as rectangular current shapes can also be applied in tACS (Antal and Paulus, 2013). In direct comparison, 10-Hz tACS was suggested to generate more focused fields than tDCS (Manoli et al., 2012), thus enabling more specific modulation of brain regions. tACS over parietal areas was found to increase working memory storage (Jaušovec et al., 2014; Jaušovec and Jaušovec, 2014), whereas tACS over prefrontal areas enhanced fluid reasoning specifically for complex tasks involving logical reasoning (Santarnecchi et al., 2013). A special form of tACS is transcranial random noise stimulation (tRNS), which applies a random electrical oscillation spectrum over the scalp, inducing increases in excitability lasting 60 min after stimulation (Terney et al., 2008). tRNS has been demonstrated to induce long-term enhancement of learning and subsequent performance on complex arithmetic tasks (Snowball et al., 2013). Compared with tDCS, tRNS led to a stronger enhancement of perceptual learning processes (Fertonani et al., 2011), which is in line with a better efficacy of tRNS compared with tDCS or tACS in clinical applications (Vanneste et al., 2013).

As an alternative to applying electrical stimulation, transcranial focused ultrasound was recently used to modulate brain function, enhancing performance on sensory discrimination tasks when applied to the primary somatosensory cortex (Legon et al., 2012, 2014). Whether transcranial focused ultrasound is capable of enhancing other higher cognitive functions still has to be determined.

Effect sizes of cognitive enhancement through brain stimulation seem to be small to modest; however, single studies also report larger effects (e.g., Chi et al., 2010). From a risk perspective, the use of noninvasive brain stimulation in research settings is largely considered unproblematic (Poreisc et al., 2007; Rossi et al., 2009). Reported side effects in healthy subjects include headaches or local pain; the most serious risk is the occurrence of seizure, often caused by incorrect stimulation parameters or the use of medications that lower the seizure threshold. However, long-term effects of noninvasive brain stimulation are currently unknown. Of particular concern are risks of premature use of the technology by lay users based on hype or speculation (Cohen Kadosh et al., 2012). Furthermore, enhancement of one cognitive function by brain stimulation might be associated with impairment of a different function (Iuculano and Cohen Kadosh, 2013).

CONCLUSIONS

Humans have always strived to increase their mental capacities. From symbolic language, writing, and the printing press to mathematics, calculators, and computers—mankind has devised and used tools to record, store, and exchange thoughts and hence enhance cognitive processes and products. In addition to such purely external devices that were designed to aid cognition, a number of tools with a more direct effect on cognitive and neural processes exist. Some behavioral cognitive enhancement strategies such as sleep or physical exercise are, to a different extent, part of our natural lives. Other behavioral techniques such as mnemonics or meditation have a long cultural tradition but must be explicitly learned. Certain psychoactive chemical enhancers such as caffeine, glucose, or other nutritional supplements also have a long history of consumption and are deeply embedded in our culture. In contrast, more modern enhancements strategies such as pharmaceuticals, computer training, or brain stimulation have raised considerable social and medical concern—not always solely based on their potential side effects and health risks. While many ethical arguments brought forward in the debate on pharmacological enhancers can also be applied to nonpharmacological enhancement strategies (Dresler et al., 2013), some arguments require a reliable comparison of the efficacy and risks of different cognitive enhancers. However, surprisingly few data that would allow comparative evaluations of different enhancement interventions exist. When comparing typical effect sizes between studies of different cognitive enhancement tools, many pharmaceuticals currently used for cognitive enhancement show rather modest effects compared with several nonpharmacological strategies. The purpose of ethical debates is not only to build possible future scenarios in which side effect–free smart pills are available to boost any cognitive capacity but also to evaluate current possibilities and constraints of cognitive enhancement. Differential and comparative research on the variety of existing cognitive enhancers is strongly needed to inform the public debate on cognitive enhancement.

ACKNOWLEDGMENTS

This work was funded by a grant from the Volkswagen Foundation, Germany. We thank Anders Sandberg, Kathrin Ohla, Christoph Bublitz, Carlos Trenados, Aleksandra Mroczko-Wąsowicz, and Simone Kühn for their contributions to earlier versions of this chapter.

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